

Amendment After Final
Application No. 10/789,105

Attorney Docket No: LP-02-019

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JAN 08 2007

I. AMENDMENTS

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1
Claim 1. (Currently Amended) A method of ~~inhibiting proteolytic conversion of inactive TGF- β to active TGF- β by a cation-independent mannose 6-phosphate (CIM6P) receptor expressed on a cytotrophoblast cell~~ improving a physiological characteristic in a pregnant female mammal, the physiological characteristic being selected from the group consisting of placental growth, placental function, placental development and placental differentiation, the method comprising administering a differentiation factor selected from the group consisting of IGF-II, a precursor of IGF-II, an isomer of IGF-II and an analog of IGF-II in an amount sufficient to promote binding of said differentiation factor to said CIM6P receptor and thereby inhibit proteolytic conversion of inactive TGF- β to active TGF- β by said receptor an effective amount of IGF-II to said pregnant female mammal in the first half of pregnancy, and thereby improve whereby said characteristic in said pregnant female mammal is improved.

2
Claim 2. (Currently amended) The method of Claim 1, wherein said administration of said differentiation factor ~~inhibits said cytotrophoblast cell from differentiating from a migratory or invasive cell type to a non-migratory or non-invasive cell type~~ effective amount of IGF-II comprises an amount sufficient to promote binding of said IGF-II to a cation independent mannose 6 phosphate receptor expressed on a cytotrophoblast cell.

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Claim 3. (Currently Amended) The method of Claim 1, wherein said differentiation factor ~~is administered to an embryo produced by in vitro fertilization for implantation into a female mammal~~ IGF-II is administered to said pregnant female mammal by subcutaneous delivery.

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Claim 4. (Currently Amended) The method of Claim 1, wherein said differentiation factor is administered to a pregnant female mammal so as to inhibit proteolytic conversion of inactive TGF- β to active TGF- β by said cytotrophoblast cells in said female mammal IGF-II is administered to said pregnant female mammal by vaginal pessary.

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Claim 5. (Currently Amended) The method of Claim 4, wherein said differentiation factor is administered to said pregnant female mammal in the first half of pregnancy IGF-II is administered to said pregnant female mammal by subcutaneous delivery and vaginal pessary.

~~Claim 6. (Cancelled)~~

6
~~Claim 7. (Currently amended) The method of Claim [[4]] 1, wherein said pregnant female mammal is selected from the group consisting of a human, a horse, a cow, a pig, a goat and a sheep.~~

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~~Claim 8. (Withdrawn) A method of preventing the implantation of an embryo in the uterine decidual endometrium, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF- β by administration of a differentiation factor selected from the group consisting of latent TGF- β , a TGF- β analogue and an antibody specific against IGF-II that inhibit the interaction between IGF-II and CIM6P.~~

~~Claim 9. (Withdrawn) A method of regulating differentiation and migration of embryonic stem cells or adult stem cells, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF- β by administration of an differentiation factor selected from the group consisting of IGF-II, an IGF-II analogue and an antibody specific against latent TGF- β that promote the interaction between IGF-II and CIM6P.~~

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Claim 10. (Withdrawn) A method of promoting terminal differentiation of embryonic stem cells or adult stem cells, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF- β and exposing said cells to reduced levels of IGF-II, whereby the stem cell CIM6P receptors are able to bind latent TGF- β and thereby promote the activation of TGF- β .

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Claim 11. (Withdrawn) A method of promoting stem cell division and stem cell migration, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF- β and exposing said cells to increased levels of IGF-II, whereby the stem cell CIM6P receptors are unable to bind latent TGF- β and thereby inhibiting the activation of TGF- β .

Claim 12. (Withdrawn) A method of diagnosing a predisposition of cytotrophoblast cells or stem cells to differentiate and migrate, the method comprising determining in a mother, father or an embryo the presence of a polymorphic form of a gene wherein the level of expression of said gene serves to regulate the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF- β and, whereby the CIM6P receptors have altered ability to bind latent TGF- β and thereby altered ability to activate TGF- β .

Claim 13. (Withdrawn) The method of claim 12, wherein said gene is selected from the group consisting of an insulin-like growth factor II gene, a urokinase plasminogen activator gene, a urokinase plasminogen activator receptor gene, a CIM6P (type-2 IGF) receptor gene, a TGF- β gene, a plasminogen gene and any polymorphic forms thereof.

Claim 14. (Withdrawn). A method of diagnosing a predisposition of cytotrophoblast cells to differentiate and migrate, the method comprising determining in a mother, father or embryo the sequence of nucleotides in the DNA near the insulin-like growth factor II gene to thereby determine the capacity of the cytotrophoblast to migrate into the uterine decidua and the capacity

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of the placenta to transport substrates to the embryo, said insulin-like growth factor II gene comprising the insulin (INS) variable number of tandem repeats (VNTR).

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Claim 15. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of messenger RNA transcribed from the insulin-like growth factor II gene in an embryo.

Claim 16. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of insulin-like growth factor II protein secreted by a mammalian embryo.

Claim 17. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of insulin-like growth factor II protein circulating in maternal and paternal blood.

Claims 18-29. (Cancelled)